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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,099	03/31/2004	**Katalin Varadi**	P-279.00	9454

7590 05/01/2008

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EXAMINER	
KOSSON, ROSANNE	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
05/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,099	VARADI ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-13,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-13,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on April 16, 2008 has been entered.

No claims have been amended, canceled or added. Accordingly, claims 1-8, 10-13 and 22-23 are examined on the merits herewith.

Claim Rejections - 35 USC § 103

Claims 1-8, 10-13, 22 and 23 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Wöber et al. (US 6,124,110) in view of Hawkins et al. (US 5,625,036), Lawson et al. ("The evaluation of complex-dependent alterations in human Factor VIIa*," J Biol Chem 267(7):4834-4843, 1992), Váradi et al. ("Monitoring the bioavailability of FEIBA with a thrombin generation assay," J Thrombosis and Heamostasis 1:2374-2380, 2003), Chan (US 5,952,198), Hogan et al. (US 6,074,826), Weinstein et al. (US 6,576,422) and Dubrow et al. (US 6,756,019), and further in view of Dou et al. (US 2002/0151582) and CRC (CRC Handbook of Chemistry and Physics 51st Ed., R.C. Weast, ed., The Chemical Rubber Co., Cleveland, 1970, p. B-77). This rejection has been discussed in the previous Office actions.

Applicants assert that the claimed invention is not obvious, because the combination of the cited references not does teach or suggest a lyophilized mixture comprising $CaCl_2$ and a fluorescently labeled thrombin substrate that forms a clear solution when dissolved in an

aqueous solution. Applicants have represented the data filed with their Declaration on September 24, 2007 with additional explanations as to how the experiments were carried out. The experiments show that when 1 M $CaCl_2$ is added to a solution of the fluorescent substrate ZGGR-AMC, in which the solvent is 10% DMSO in water, a precipitate forms. Applicants assert that, therefore, one of ordinary skill in the art would have had no expectation of success in combining the cited references to produce the claimed invention.

In reply, the scope of the instant claims is much broader than the data presented in the experiments. The claims recite that the reagent in the claimed kit and method is a lyophilized preparation of any amount of calcium chloride and any amount of any fluorescently labeled thrombin substrate that is aliquotted or packaged in any way. Thus, the claims encompass kits in which amounts for each blood sample to be tested are placed in test tubes or wells of a microtiter plate, amounts of the thrombin substrate and of calcium chloride that do not require further dilution and are, as a result, much smaller than the amounts in a stock solution concentrate, as in Applicants' experiments. Applicants' experiments were carried out with one mixture that is not a rehydrated lyophilized preparation. This mixture contains 5 mM ZGGR-AMC in a buffer of 10% DMSO, 25 mM HEPES and 175 mM NaCl (7.4 or 74 ml) to which 1 M calcium chloride (0.55-0.58 or 6 ml) is added for a final concentration of about 72 mM. Applicants note that the substrate is shaken or stirred to form a solution. When the calcium chloride is added, a precipitate forms that may be dissolved by stirring, shaking and/or heating and that reforms upon standing. But, the data show considerable variability in the degree of turbidity measured in the samples (particularly in Table 3 of Experiment 2), and the amount of turbidity increases when the samples are contained in the wells of a microtiter plate vs. in vials. Thus, the container for the assay reagent is also a factor. The instant claims do not recite an

assay reagent that is a product by process, the process that Applicants used to make the fluorescent thrombin substrate-calcium chloride reagent that was tested in Experiments 1-5.

As previously discussed, in contrast, in the assay reaction mixtures of Váradi et al., the concentration of ZGGR-AMC is less than 0.5 mM, and 15 mM $CaCl_2$ is added, although the volume of this solution used is not disclosed. Thus, the concentration of $CaCl_2$ is below 15 mM (see p. 2375, right col.). In the assay reaction mixtures of Lawson et al., the concentration of $CaCl_2$ is 5 mM, and the concentration of the fluorescent substrate (m-LDR-nds) is less than 1 mM (see p. 4836, right col., second and third full paragraphs). These references do not indicate that anything precipitates during any step of the assays. The claims do not recite any quantitative amounts for the fluorescent thrombin substrate and the calcium chloride in the claimed kit, and the prior art teaches quantitative amounts of these reagents that may be used without a problem of reagent precipitation. Applicants' results may be due simply to using more concentrated solutions of $CaCl_2$ and ZGGR-AMC than in the prior art. Thus, the data in these experiments do not serve to overcome the obviousness rejection.

Applicants note that the subject matter of Váradi et al. is their own work, that the reference does not disclose that DMSO is required to dissolve the fluorescently labeled thrombin substrate, although the DMSO is required, and that the reference does not disclose that a precipitate forms when the calcium chloride solution is added, although a precipitate does from. Applicants assert that it would not be expected that an organic solvent could be omitted when reconstituting the lyophilized mixture of the fluorescently labeled thrombin substrate and calcium chloride. Applicants note that their kit is "ready to use."

In reply, the comprising language of the claimed kit and method does not exclude an organic solvent or the step of adding a buffer comprising an organic solvent to dissolve the lyophilized mixture. An aqueous buffer containing 10% DMSO is still an aqueous solution. As

for "ready to use," the reagents taught by the combination of the cited references are also "ready to use." The cited references disclose fewer steps than Applicants for preparing these reagents. As discussed above, the claims are much broader than the disclosure of Váradi et al., who disclose only one assay mixture of a fluorescent thrombin substrate (ZGGR-AMC) and calcium chloride. One of ordinary skill in the art at the time of the invention would have been able to identify and prepare suitable solutions or buffers for the claimed kit and would have been able to determine suitable concentrations for the reagents in the claimed kit so that a thrombin generation time could have been measured in patient samples using the claimed kit. As noted above, if rehydrating the mixture of calcium chloride and the fluorescent thrombin substrate did require a small amount (or a certain amount) of an organic solvent in the water to dissolve the substrate, the claims do not exclude this feature.

As for lyophilizing solutions of calcium chloride and the fluorescent thrombin substrate together vs. separately, Examiner's point was that the prior art teaches that each of the two may be lyophilized separately. It would have been obvious to one of ordinary skill in the art at the time of the invention to mix the two solutions and lyophilize them together, because the artisan of ordinary skill would have known that combining the reagents in a kit wherever possible provides efficiency in the preparation of the kit and in the use of the kit. Applicants have not shown that any difference results from lyophilizing these two reagents together vs. separately.

In view of the foregoing, the rejection of record is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652
rk/2008-04-22

/Rebecca E. Prouty/
Primary Examiner,
Art Unit 1652